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Etoposide/Carboplatin chemotherapy for the treatment of metastatic myxomatous cerebral aneurysms

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Dear Sirs,

Myxomas comprise the majority of cardiac tumors [1]. Patients may experience signs of cardiac obstruction or systemic embolism, accompanied by non-specific systemic symptoms such as fever or malaise, [2]. Embolization to the central nervous system is common. However, while embolic stroke due to cardiac myxoma is treated by tumor resection, delayed neurological complications may arise from metastatic spread of myxomatous cells into the brain, causing either aneurysms or solid tumor growth. In these rare cases, the clinical course is often complicated and an effective therapeutic regimen has not yet been established (Online Resource 1) [3-10].

A 41 year-old female patient was referred, following a brain magnetic resonance imaging (MRI) scan for the diagnostic work-up of new-onset, “burning” headaches and increasing fatigue. MRI showed multiple, acute and subacute T2-hyperintensities suggesting a proximal embolic source or possibly vasculitis (Online Resource 1). Routine blood results, spinal fluid analysis and conventional angiography were unremarkable. Transesophageal echocardiography (TEE) revealed a 5.2. x 2.6 mm left atrial tumor. The tumor was resected, and histologic examination confirmed the diagnosis of a cardiac myxoma (Figure 1 A, B).

After an uneventful postoperative period, the patient reported the new onset of pounding headaches about one year later. Follow-up MRI demonstrated the presence of microbleeds and multiple fusiform aneurysms (Figure 2 A). TEE was repeated, but no recurrence of the cardiac myxoma was found. At the same time, the patient suffered from recurrent simple focal seizures and a mild, sensorimotor paralysis of the left arm. Angiography now revealed the presence of multiple fusiform aneurysms (Figure 2 G). Biopsy of the largest aneurysm in the right pre-central region demonstrated intramural and intravascular collections of neoplastic spindle cells embedded in myxoid material, along with blood extravasation and perivascular lymphoplasmacytic infiltrates consistent with metastatic emboli of the previously resected (> 1 year before) cardiac myxoma (Figure 1 C). Five months later, the patient

reported progressive loss of function of the left hand and severe, burning headaches. Follow-up MRI demonstrated a dramatic progression of the aneurysms and hemorrhages (Figure 2B). 18F-Ethyltyrosine (FET)-PET showed metabolic activity within the largest aneurysm suggestive of a neoplastic focus (Figure 2 H). At this time, combined chemotherapy with etoposide (100 mg/m^2 body surface area, days 2 and 3) and carboplatin (240 mg/m^2 body surface area, day 1), administered over a three-day period in addition to 4 mg/d dexamethasone was started. After two cycles, the patient showed major clinical improvement. MRI confirmed a reduction in hematoma volumes and brain edema, and stable aneurysm size (Figure 2 C). However, two months after conclusion of six cycles of etoposide/carboplatin, administered in 4-week intervals, control MRI again revealed increased size and contrast enhancement as well as edema progression of the largest right pre-central aneurysmatic lesion (Figure 2 D). To prevent further damage from bleeding and pressure effects, this lesion was surgically resected (Figure 2 E). The resected tissue specimen revealed ongoing myxoma invasion and an even more pronounced inflammatory reaction (Figure 1 D-G). Therefore, three weeks after surgery, the patient was started on immunosuppressive and anti-inflammatory therapy with i.v. cyclophosphamide (600 mg/m^2 body surface area). She has received four cycles so far, and remains clinically stable on 1.5 mg dexamethasone, which will be slowly tapered off. Recent angiography and MRI have confirmed stable aneurysm size and distribution (Figure 2 F, J).

In cases of severe neurological impairment due to multifocal myxomatous aneurysms, where a wait-and-see strategy is not a reasonable therapeutic option, chemotherapy may stabilize disease progression. Longer follow up is needed to evaluate whether disease control with the cyclophosphamide regimen proves superior to other agents.

Conflict of Interest Statement

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Figure Legends

Figure 1: Histological analysis of cardiac tumor and cerebral aneurysms

(A): The papillary aortic tumor is dominated by a paucicellular myxoid background. (B): In addition to the stellate tumor cells, scattered plasma cells and lymphocytes are embedded in the myxoid stroma. (C) Although more cellular, the first brain metastasis demonstrates the unmistakable histological features of myxoma. A mitotic figure is present (arrowhead). (D, E): Microscopic examination of the second brain sample reveals a large, aneurysmal dilatation of the sampled artery, with intramural and intraluminal infiltrates of small, bland spindled tumor cells embedded in a myxoid matrix (arrowheads). Dense chronic inflammation is seen surrounding the vessel and scattered inflammatory cells are found within the myxoma (arrows in E). (F): The Elastica-von-Gieson stain shows disruption of the internal elastic lamina (arrowheads) at the base of the aneurysm. (G): Higher magnification shows sparse mitotic activity of the tumor cells (arrowhead).

(A, E): hematoxylin-eosin, scale bar = 200 µm. (B): hematoxylin-eosin, scale bar = 100 µm. (C, G): hematoxylin-eosin, scale bar = 50 µm. (D): hematoxylin-eosin, scale bar = 1 mm. F): Elastica-von-Gieson, scale bar = 1 mm.

Figure 2: Myxomatous aneurysms in the brain: multimodal imaging

A-F: T2- (upper panel) and T1- weighted, contrast enhanced images (lower panel) demonstrating the growth of the aneurysms as well as extension of hemorrhage and edema before (A, B) and after (C, D, E) chemotherapy with etoposide/carboplatin and cyclophosphamide (F), which was started in 09/2013. In August 2013 (between D and E), the large aneurysm on the right pre-central region was surgically removed. G: Conventional angiography from 8/12 with multiple fusiform aneurysms (red arrow), some still detectable after etoposide/carboplatin chemotherapy in 8/13 (I).

J, H: FET-PET maps of a slice corresponding to the images above before (J) and after (H) etoposide/carboplatin chemotherapy. FET accumulation is not significantly reduced after treatment.

Figure 1
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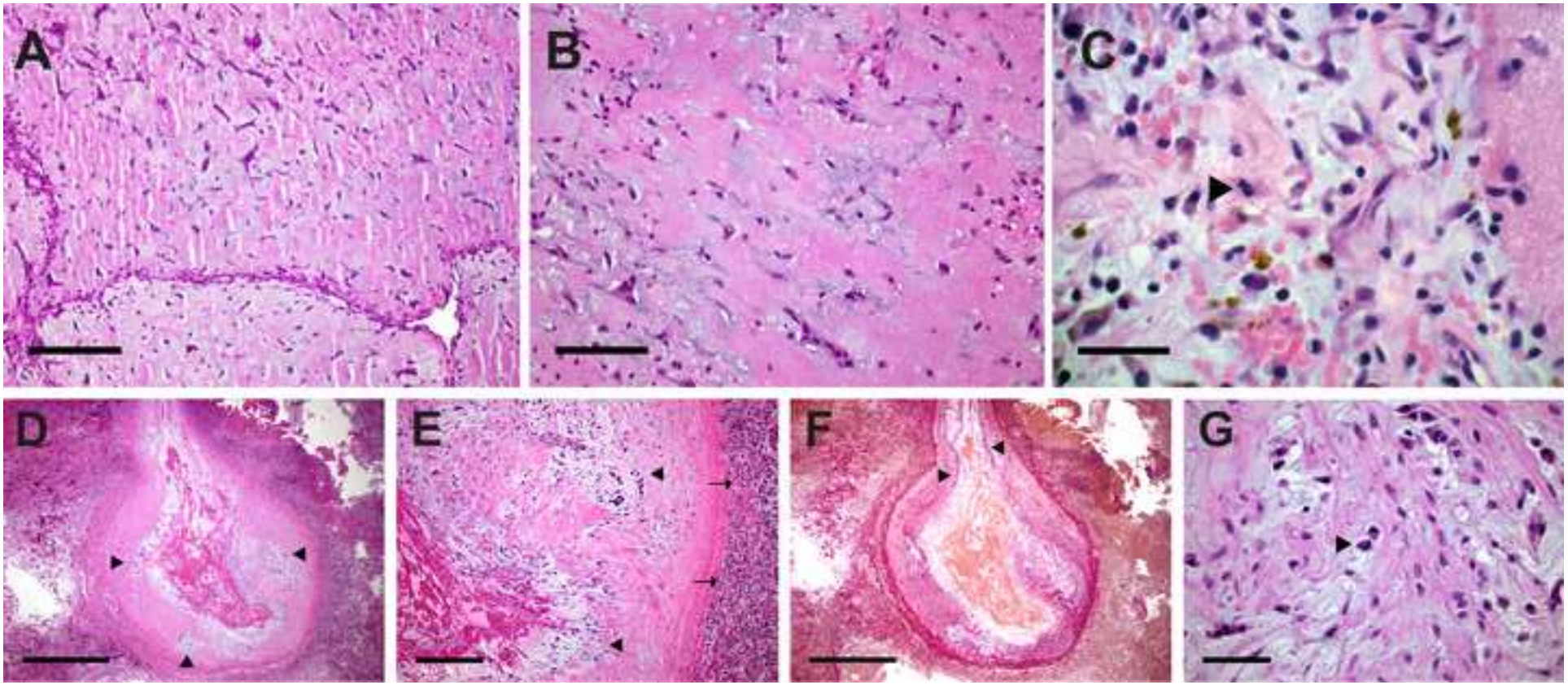

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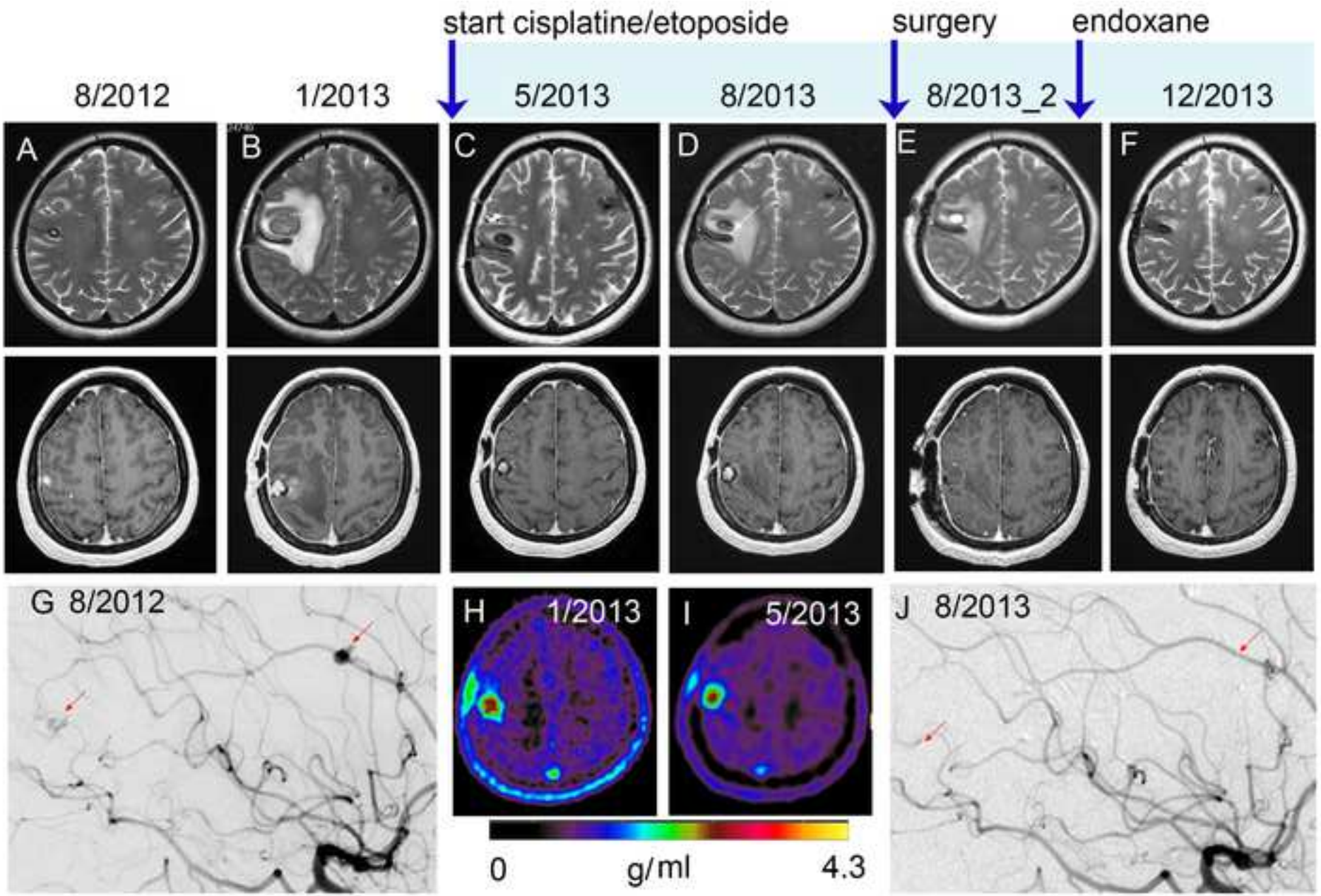

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